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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,467	10/05/2001	Leonard Buckbinder	PC10850B	4966

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,467	BUCKBINDER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2002 and 25 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4 and 15-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4 and 15-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10&13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/08/02 (Paper No. 12), is acknowledged.

2. Claims 3-4 and 15-32 are pending and currently under examination.

3. The disclosure stands objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification on page 1, lines 13, contains hyperlinks. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference.

4. Please see form PTO-948, mailed on 7/02/02 (Paper No. 9) for the Draftsperson comments on views not labeled separately for Figures 1 and 3. Applicants are required to amend the Brief Description of the Drawings on pages 7 and 8 to reflect the changes.

5. The amendment filed 10-05-01 stands objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The "incorporated by reference" to U.S. application serial no. 60/191,382 on page 1 of the specification does not enjoy the status as part of the original disclosure in the application because the amendment is not referred to in the oath.

6. The oath or declaration stands defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the oath does not refer to the preliminary amendment filed 10/5/01.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 3-4 and 15-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide or a composition of SEQ ID NO: 2 encoded by SEQ ID NO: 1 and a metalloproteinase (aa 289-478 of SEQ ID NO:2), disintegrin (aa 509-578 of SEQ ID NO:2) domain, and thrombospondin (aa 589-642 of SEQ ID NO:2)

domain thereof for identifying a substrate for ADAMTS-S1, does not reasonably provide **enablement** for any polypeptide having an amino acids sequence comprising an amino acid sequence having at least 90%, 95%, 97% or 99% identity to the amino acid sequence of the metalloproteinase domain or the prodomain of SEQ ID NO:2 in claims 3, 16, 17, 21-26; any polypeptide which comprises an amino acid sequence that is a metalloproteinase, disintegrin domain, prodomain, or thrombospondin domain of SEQ ID NO: 2 in claim 4; or a pharmaceutical composition for the treatment of the disease recited in claim 15, any peptide comprising amino acids 289-478 of SEQ ID NO: 2 in claim 19, or amino acids 19-287 of SEQ ID NO: 2 in claim 20, or any polypeptide having 5-10, 1-5, 1 amino acids substituted, deleted or added, or combinations of such changes in claims 27-31 or any polypeptide of claim 21 having 1-5 conservative amino acid substitutions in claim 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim essentially for the same reasons set forth in the previous Office Action, paper No. 9, mailed 7/02/02.

Further, claims 27-32 recite amino acid modification. However, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions, addation and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

9. Claims 3 and 15-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the same reasons set forth in the previous Office Action, paper No. 9, mailed 7/02/02.

Applicant's arguments, filed 11/8/02 (Paper No. 12), have been fully considered, but have not been found convincing.

Applicant argues that by amending the claims to at least 90% identity has addressed the bases of the enablement rejection. Further, Applicant provides the same argument for the written description.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. For example, 90% identity to amino acids 289-478 of SEQ ID NO: 2, counts for 19^{20} different variation (i.e. 3.8 X 10^{25} species). It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated amino acids having " at least 90%, 95%, 97% or 99% identity" or "amino acids substitution, deletion, addition or combinations" or any polypeptide comprising "amino acids 289-478 of SEQ ID NO:2 or amino acids 19-287 of SEQ ID NO: 2" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of ADAM-S1, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, making changes up to 10%, 5 %, 3% or 1% of a polypeptide sequences does not provide that the protein will retain the same metalloproteinase activity as the unmutated polypeptide. One of ordinary skill in the art cannot envision all of the amino acid and amino acid substitutions, deletions, additions or combination encompassed by the breadth of the claims and having metalloproteinase activity.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

11. Claims 3-4, 16-17, 19, 21-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagase et al (March 14, 2000) (GenBank Accession No. AB037733) essentially for the same reasons set forth in the previous Office Action, paper No. 9, mailed 7/02/02.

Applicant's arguments, filed 11/8/02 (Paper No. 12), have been fully considered, but have not been found convincing.

Nagase *et al* teach a polypeptide which comprises an amino acid sequence that is a metalloprotenase at positions (131-320), disintegrin domain at positions (aa 353-423) and thrombospondin at positions (aa 433-487) and prodomain at positions (aa 143-262) as recited in instant claim 4. The terms "comprising" and "comprises" in 3 and instant claim 4 are open-ended. They would open up the claim to include the reference 1,471 polypeptide molecule.

Claims 27-32 are included because the reference polypeptide sequence "having" additional 1, 1-5 and 1-10 amino acids, furthermore, "comprising" and "having" in base claims 21 and 22 are open-ended teams, which would open up the claims to include the 1, 471 polypeptide molecule.

Applicant argues that the GenBank sequences can be updated and that the content of the original sequence may not be readily apparent from inspection of the database.

However, Examiner notes that this is the only GenBank version of the sequence that appears to be available, unlike those situations where the sequence has undergone multiple revisions.

12. The following new ground of rejection is necessitated by the IDS submitted on 11/8/02.

13. Claims 3-4, 16-17, 21-32 are rejected under 35 U.S.C. 102(e1) as being anticipated by WO 200111074 A2 (IDS Ref. No. A1).

The `074 publication teaches a 1,934 amino acid polypeptide that is 99% identity to SEQ ID NO: 2 which comprises an amino acid sequence that is 99% identity to the claimed metalloprotenase at positions 289-477, 99% identity to claimed prodomain at positions 19-287, 96% identity to claimed disintegrin domain at positions 348-417 and 100% identity to claimed thrombospondin motif at positions 588-641.

Claims 27-32 are included because the reference polypeptide sequence "having" additional 1, 1-5 and 1-10 amino acids, furthermore "comprising" and "having" in base claims 21 and 22 are open-ended teams, which would open up the claims to include the 1, 934 polypeptide molecule.

The reference teachings anticipate the claimed invention.

14. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 sent with Paper No.9, mailed 7/02/02.

15. It appears that the polypeptide of SEQ ID NO: 2 is free of prior art.

16. No claim allowed

17. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 11/8/02 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
3/20/03